the entire circumference of the glow of a particle rapidly vibrating throughout a space very many times its own actual dimensions.

These ointments are also undergoing clinical tests and investigations. It may be of interest, however, to report that the toxicity of colloidal oil-soluble mercury, as determined upon guinea pigs, compared with ordinary metallic mercury appears to be about four times as great. The bactericidal power of water-soluble colloidal mercury has also been determined and appears to be equivalent to a phenol-coefficient of about 27.7.

Here also are samples of water-soluble colloidal copper, protected with casein, and ampoules of the aqueous solution ready for hypodermic or intravenous injection. Each ampoule contains 10 milligrams of substance corresponding to 2 milligrams of metallic copper, this quantity being the mimimum lethal dose for 250 gm. guinea pigs. All these metallic colloids have been produced by the reduction method, starting with soluble salts.

Without doubt many things remain to be learned by the employment of these products in medicine, and the earnest co-operation of careful laboratory and clinical investigators along these lines may lead to discoveries of untold importance in the treatment of disease.

RESEARCH LABORATORY OF H. K. MULFORD COMPANY, July 28, 1913.

A PHARMACODYNAMIC STUDY OF THE PITUITARY GLAND WITH TESTS OF A NEW PRODUCT.

FRITZ HEIDELBERG, PAUL S. PITTENGER AND CHARLES E. VANDERKLEED.

The role which the pituitary body or hypophysis plays in life has until recently been a mystery. It was at first thought that its function was to lubricate the nasal cavities. This belief, however, was soon discarded and replaced by the supposition that the gland was, like the appendix, of no use at all. Later, however, it was proven by Vassale and Sacchi,[1] Caselli[2], and others that the gland plays a very important role and is absolutely necessary to life. It has also been found that acromegaly and other diseases are due to functional disturbances produced by an over or an under secretion of this gland, and that its removal causes death. According to Sajous[3] the anterior lobe may prove to be the center of the adrenal system.

The pituitary body varies in size according to the age and species of the animal. The gland most commonly used in therapeutics is that obtained from the ox, and is about ¾ inch in diameter.

The gland is composed of two parts or lobes,—the anterior and the posterior or infundibular. The smaller or posterior lobe, which forms only about ten to fifteen percent of the total gland, is the more important therapeutically. This

[1] Vassale and Sacchi: Rivista Sperimentale de Freniatria p. 83, 1894.
[2] Caselli: Studii anatomici e sperimentali sulla Fisiopatologia della Glandola pituitaria, 1900.
[3] Sajous: Internal Secretions and the Principles of Medicine. Vol. 1, p. 216.

lobe contains practically all of the active principles while the anterior lobe is the one which is so necessary to life.

The total pituitary body contains about 80 percent of water, or in other words 100 parts of the fresh gland give about 20 parts of dry substance, containing 2 to 3 parts of the posterior lobe.

Knowledge concerning the chemical composition of the pituitary gland has only recently gained proportions sufficient to warrant the hope that science will ultimately be as successful in isolating and synthesizing its active principle or principles as it has been with the suprarenal gland. Owing to the similarity existing between the physiologic actions of the pituitary and those of the suprarenal gland the theory has been advanced that the active principles of the former will be very similar to epinephrine. In fact it has been shown that the activity of the gland can be concentrated into a basic fraction forming salts with acids. It was possible, however, to split this basic fraction into several fractions of different chemical properties (Fuhner)[4], which would tend to prove that the action of the pituitary body is due to not one but to the combined actions of

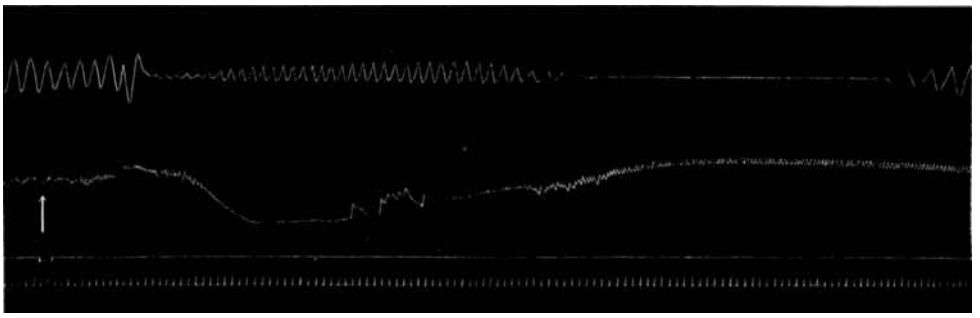

FIGURE 1.—Cut of Prof. Führer's tracing showing the action of the basic fractions, tested by him, on blood pressure (negative).

several active principles. Schäfer and Vincent[5] had also shown sometime before that the blood-pressure-raising principle could be divided into two fractions by their different solubilities in alcohol, one containing a pressor and the other a depressor action.

Practically all of the commercial preparations of pituitary on the market are claimed to be extracts of only the posterior lobe. Since the process of separating the posterior from the anterior lobe is both very tedious and expensive, the object of our endeavors has been to isolate from an extract of the whole gland, either a highly active fraction or the active principles themselves. We have also been concerned in endeavoring to differentiate between extracts or solutions claimed to be prepared from certain portions of the gland, and those from the gland as a whole, as we doubt very much whether, in all cases, preparations said to be made from the posterior portion are really not prepared from the gland as a whole.

Physiologic experiments have demonstrated that extracts of this gland are

[4] Fuhner: Hypophyse deutschen medizinsche Wochenschrift, March, 1913, p. 491.

[5] Schäfer and Vincent: Journal of Physiology, May 11, 1899.

valuable therapeutic agents. Thus Magnus and Schäfer[6] and Schäfer and Herring[7] have shown that it accelerates diuresis; Oliver and Shäfer[8] that it is valuable for raising the blood pressure by arterial constriction; Dale[9], Bell and Hicks[10], and v. Fränkl Hochwart and Frohlich[11] that it excited marked uterine contractions, Ott and Scott[12] that it possesses a rather marked galactagogue action.

The scant knowledge of the chemical composition of the gland and extracts of the same, renders it impossible to ascertain by chemical means the comparative value of two or more extracts or fractions. We are therefore compelled to resort to physiologic assay methods. Of the various physiologic actions of the gland above mentioned there are three which present themselves as possible means of

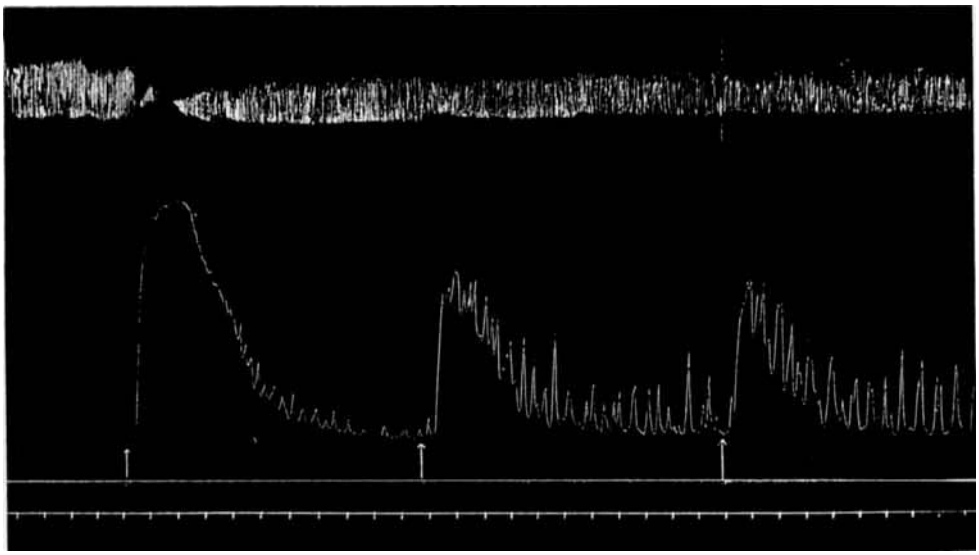

FIGURE 2.—Cut of Prof. Fühner's tracing showing marked uterine contractions produced by the same preparation which gave negative results by the blood pressure method (See Figure 1).

physiologic standardization, i. e., the action of the blood pressure, the uterus, and the kidneys.

The fact that the blood-pressure method involves the simplest *technique* together with its satisfactory and almost universal use as a means of standardizing epinephrine and suprarenal extracts would at first lead one to believe that this method would also be the most satisfactory one for standardizing pituitary extracts. It has, however, serious disadvantages in case of the latter. As before stated, the blood-pressure-raising principle can be divided into two parts, one

[6] Magnus and Schäfer: Proc. Phys. Soc., p. IX, 1901.
[7] Schäfer and Herring: Phil. Trans., 1906 B.
[8] Oliver and Schäfer: Journ., of Phys., XVIII, p. 277, 1895.
[9] Dale: Biochem. Journ., IV, p. 427, 1909.
[10] Bell and Hick: Brit. Med. Journ., i. p. 777, 1909.
[11] v. Fränkl Hochwart and Fröhlich: Arch. f. exp. Pathol., u. Therapie, LVII, p. 347, 1910.
[12] Ott and Scott: Proc. Soc. exp. Biol., New York, 1910.

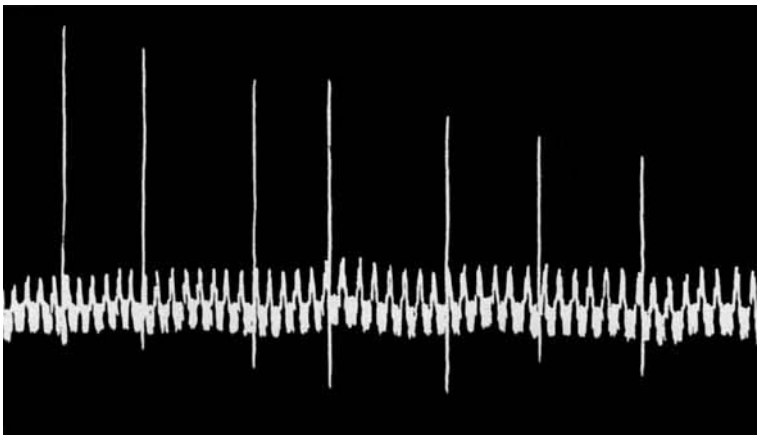

FIGURE 3.—Shows the gradual decrease in the rises in blood pressure produced by repeated injections of equal sizes.

possessing a pressor and the other a depressor action. Prof. Führer of Frieburg[18] has also shown that the sum of the basic principles tested by him caused marked uterine contractions and only a slight pressor action, which was almost completely masked by a marked preliminary depressor action.

Furthermore, extracts which had been deprived of their depressor action by fractionation with alcohol, showed marked pressor effects, while on the other hand they were sometimes almost entirely free from action upon the uterus.

Another serious drawback to the blood-pressure-raising method, is the fact that the active principles of pituitary extract are not nearly as rapidly oxidized as those of the suprarenal gland and therefore repeated injections of equal sizes produce unequal rises,—the subsequent ones generally showing a waning of the pressor action and an increasing prominence of the preliminary depressions.

Still another objection to the blood pressure method is its comparatively low

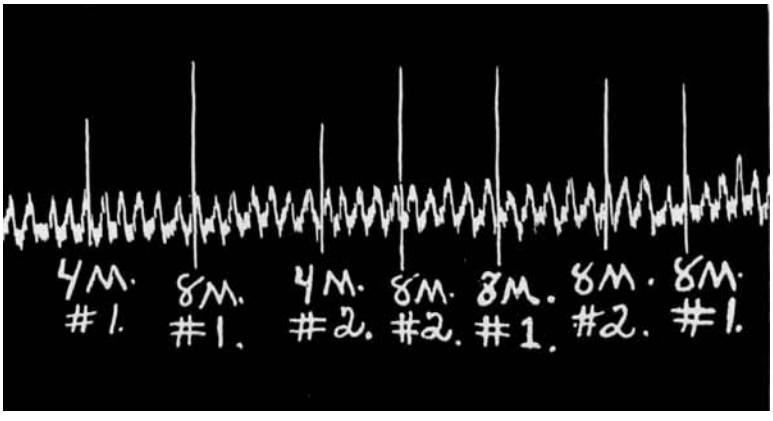

FIGURE 4.—Tracing showing equal rises in blood pressure from equal amounts of the two extracts mentioned above.

[18] Hypophyse deutschen medizinische Wochenschrift 1913, No. 11, p. 491.

sensitiveness; in other words, it requires, in most cases, a rather large variation in the size of the injection to produce a variation in the resultant rise. This latter objection is especially serious when comparing two or more samples for research purposes, in which case a mistake of 20 to 30 percent in interpreting the results of an assay may cause a considerable loss of time. For example, we had occasion during our experiments to compare two extracts made by different processes, in order to determine which was the better of the two. According to the blood-pressure method both extracts showed the same activity, while when

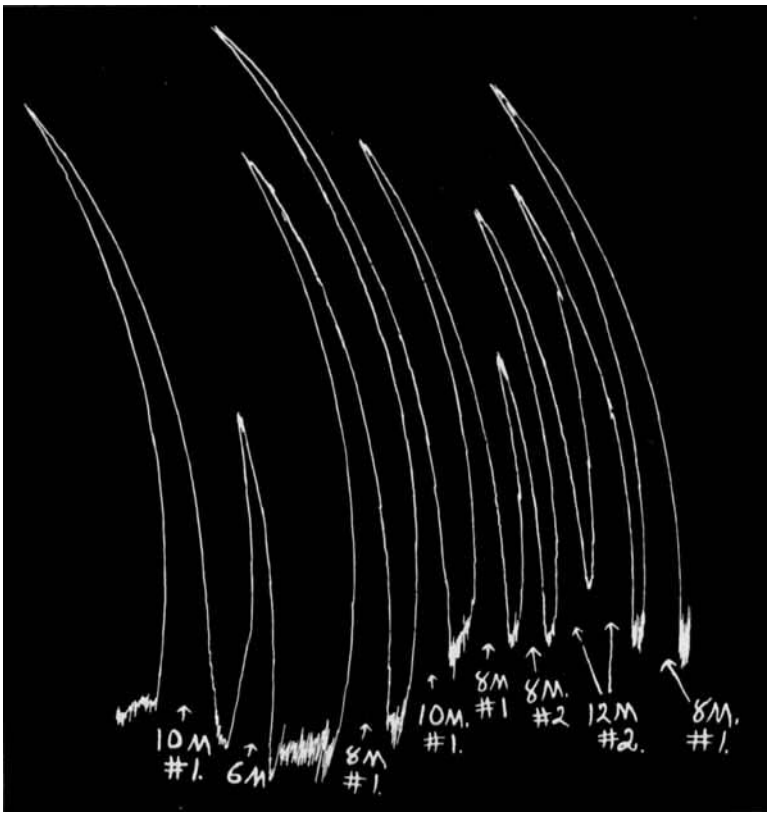

FIGURE 5.—Tracing proving the sensitiveness of the uterine method. Chart shows 8 minims of extract No. 1 to be stronger than 12 minims of extract No. 2. By the blood pressure method (owing to its lower sensitiveness) both preparations showed the same activity (See Figure 4).

tested by the uterine method, which is far more sensitive, 8 minims of one extract prove to be more active than 12 minims of the other. (See Figures 4 and 5).

We have had no experience with methods of standardization based upon the diuretic action, but it has been shown by Dale and Laidlaw[1] that this method is also unsatisfactory, due to the tolerance produced by the first injection. They

[1] "A Method of Standardizing Pituitary (infundibular) Extracts," by Dale and Laidlaw. Journ. Pharm. and Exp. Ther., Sept., 1912, p. 75.

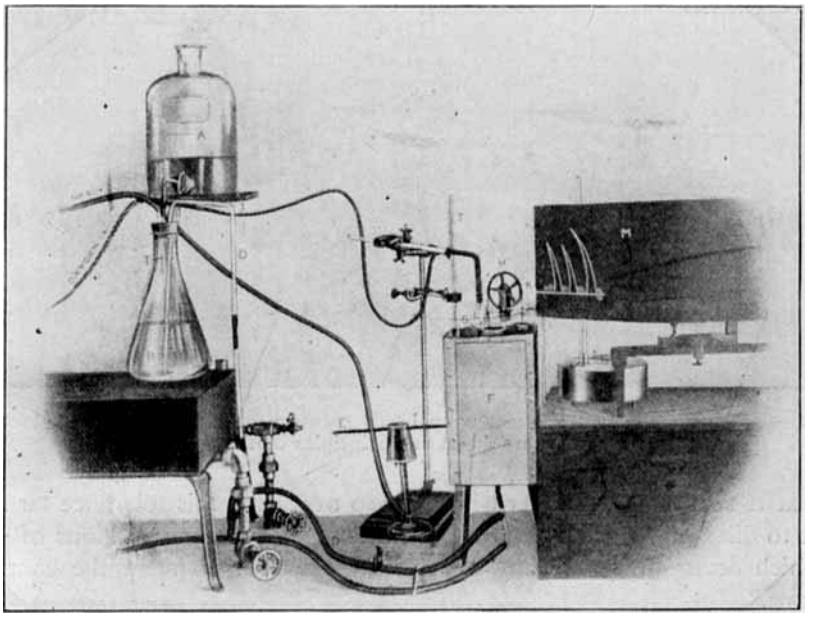

FIGURE 6.—Apparatus employed for testing ergot and pituitary extracts upon the isolated uterus of virgin guinea pigs.

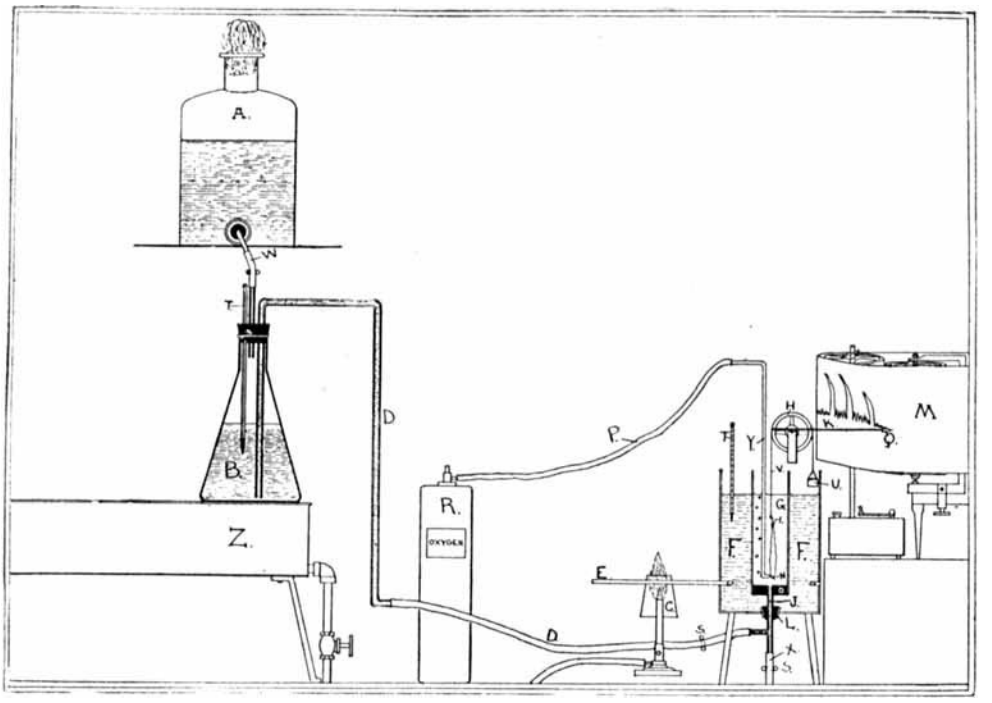

FIGURE 7.—A graphic illustration of the above apparatus.

A—Aspirator bottle containing Ringer's solution; B—Ringer's solution; Z—Steam bath; D—Syphon tube carrying Ringer's solution to cylindrical vessel; F—Constant temperature bath; E—Brass rod; C—Bunsen burner; G & N—Hooks suspending uterus; O—Rubber stopper; X—Tube leading to waste pipe; U—Counter balancing bucket; H—Escapement wheel; K—Writing lever; Q—Writing point; M—Kymograph; T—Thermometers.

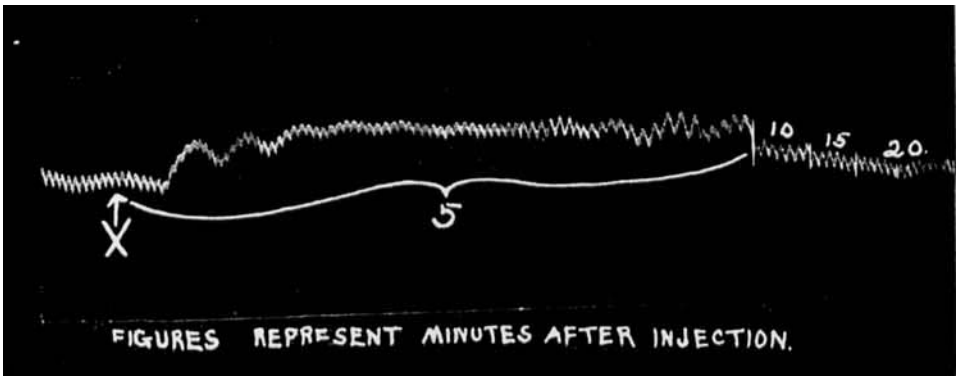

FIGURE 8.—Tracing showing the effect upon blood pressure of intravenous injections of our metallic derivative of the active principles of the whole gland.

state that if small doses are used in order to overcome this tolerance "it may be difficult to distinguish genuine effects from the spontaneous variations of urinary flow which occur in almost any experiment, however constant the controllable conditions."

In our experiments upon the isolated uterus we carried out essentially the method of Dale and Laidlaw with a few modifications of the apparatus employed. We used the same apparatus that we employed in our researches upon ergot, as set forth in another paper[2].

We have used both the uterine and the blood pressure method, during the

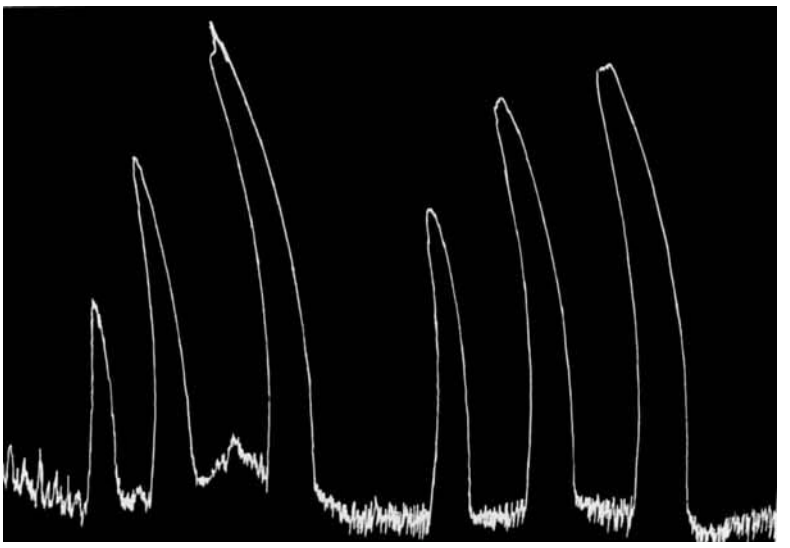

FIGURE 9.—Tracing showing the effect of our metallic derivative of the active principles of the whole gland upon the isolated uterus of the virgin guinea pig.

[2] "A New Uterus Contraction Method of Testing Ergot,—with comparison with the blood pressure method," by Pittenger and Vanderkleed.

past year, throughout all our researches on pituitary substances, and are thoroughly convinced that the uterine method is by far the better of the two. We will not go into a detailed description of the advantages of the uterine method, as our results agree in every instance with the claims made for it by Dale and Laidlaw.

In our experimental work on pituitary extract, we have succeeded in preparing colorless extracts of the *whole gland,* possessing all of the characteristic physiologic properties of the posterior lobe. Such a solution, in sterile ampul form, is here shown, together with tracings, showing the characteristic blood-pressure-raising power, and also the uterus-contracting power, peculiar to the posterior lobe, to a marked degree.

This solution has been prepared as follows: First a watery extract is made of the whole gland. This is then purified by a series of precipitations which deprive the extract of practically all inert proteid substances. This purified extract is then treated with metallic salts of aluminum (or other suitable metals), after which it is neutralized, thus precipitating the metallic derivative. This precipitate is then filtered off, washed, and dried. An aqueous solution of this dried material forms the solution exhibited in the ampoules. The product, therefore, is in reality a solution of a metallic derivative or derivatives of the active principles, in the purification of which, the presence of the relatively inert anterior lobe seems not to interfere, thus permitting of a great saving in the labor and resultant expense of separating the lobes.

We have not yet been able to determine exactly the nature of these metallic derivatives, but are continuing our researches and will give more detailed accounts of further experiments in subsequent papers.

RESEARCH LABORATORY OF H. K. MULFORD COMPANY, August 13, 1913.

VARIATION IN SUSCEPTIBILITY OF THE GUINEA PIG.

(Continuation of a previously reported study.)*

CHAS. E. VANDERKLEED, PHAR. D., AND PAUL S. PITTENGER, PHAR. D.

In a paper read at the 1912 meeting of the American Pharmaceutical Association in Denver, the results of a series of experiments covering one year were given, in which it was shown that the average minimum lethal dose of crystallized strophanthin, Thoms, (ouabain) for 250 gm. guinea pigs, varied during the course of the year from 0.0000511 gm. in September, 1911, to 0.0000844 gm. in May, 1912, the average for the year being 0.0000661, and the extreme variation ranging from 22.7 percent below to 27.7 percent above this average. These experiments having conclusively shown that sex and weight may be dismissed as unimportant, this conclusion having been fully concurred in by other investi-

*Variation in the Susceptibility of the Guinea Pig to the Heart Tonic Group, (Second Paper), by Chas. E. Vanderkleed, Phar. D., and Paul S. Pittenger, Phar. D., Journal of the American Pharmaceutical Association, II, May, 1913, p. 558.